

REMARKS

This Amendment is responsive to the non-final Office Action of November 17, 2003. Applicant submits concurrently herewith a Petition for a two-month extension of time along with the required fee, accordingly this Amendment and Response is deemed to be timely filed. Applicant respectfully requests reconsideration of the subject application in view of the foregoing claim amendments and the following remarks:

The Applicant wishes to thank Examiners Srivastava and Tate for the telephonic interview in this matter on February 24, 2004. During the interview, a set of proposed claims in response to the outstanding Office Action were discussed.

I. Status of Claims

Claims 1-11 are pending in the application and these claims stand rejected.¹

Claims 3-5, 7 and 10 have been amended to clarify the invention. New claims 12-21 have been added.

Support for the new claim 12 can be found in the specification, for example, at page 4, lines 16-26. Support for the new claim 19 can be found in the specification, for example, at page 7, lines 29-31. No new matter is added.

II. Priority

The Examiner notes on page 2 of the Office Action that claims 1-2 and 4-11 are accorded the priority date of 08/15/2002, not 09/21/1999, which is the date of priority under 35 U.S.C. 119(e). Applicant respectfully traverses the Examiner's assertion at least to the extent that the Examiner construes the date of 08/15/2002, which is the date of receipt of 35 U.S.C. 371(c) requirements, to be the filing date for the instant national stage application. Applicant respectfully points out that the instant 10/088,664 application is a U.S. national stage of PCT/US00/25733 application and the filing date for this national stage application is 9/20/2000,

¹ The Office Action Summary sheet indicates that claims 1-11 are objected to.

which is the filing date of the PCT application. See, 37 C.F.R. § 1.53(j).

III. Rejection Under 35 U.S.C. § 112, 1st Paragraph, Enablement

Claims 3-11 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to satisfy enablement requirement. Claims 5, 7 and 10 separately stand rejected for the same reason. Specifically, the Examiner contends that the specification is enabling only for a method to treat cancer or to reduce the incidence of cancer by administering a composition comprising resveratrol but not for a method to prevent cancer by administering the claimed composition. Applicant respectfully traverses these rejections.

As a preliminary matter, Applicant believes that the enablement rejection is incomplete. When rejecting a claim under the enablement requirement of § 112, the examiner bears the “initial burden.” The case law makes clear that properly reasoned and supported statements explaining failures to comply with § 112 are a requirement to support a rejection. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Applicant respectfully believes that these requirements are not met. For example, the Examiner states that “APPLICANTS HAVE NOT DEMONSTRATED THE CLAIMED FUNCTIONAL EFFECT OF TREATING AND/OR PREVENTING ANY AND ALL LOW-RENIN HYPERTENSION, SALT-SENSITIVE HYPERTENSION OR LOW-RENIN, SALT SENSITIVE HYPERTENSION.” There are no such disease conditions recited in the claims. It is thus unclear whether the paragraph bridging pages 3 and 4 of the Office Action is intended for claims reciting such disease conditions.

In rejecting claims 3-11, and claims 5, 7 and 10 separately, the Examiner seems to be arguing that the instant Application has enabling data only with respect to the use of resveratrol in achieving lesser incidence of cancer and points to specification page 12, line 4 to page 13, line 16. Applicant respectfully submits that the specification has more than just this data. The specification has data sufficient to enable other claims directed to both prevention and treatment of cancer using a mixture of isolated polymethoxylated flavones set forth in claim 1. Claim 3, for example, is directed to a method for inhibiting tumor cell growth in an animal comprising administering to the animal the extract of claim 1. The specification’s teachings, for example, at

page 4 line 27 through page 5, line 6 fully support such claims. It provides *in vivo* animal model data showing 0% tumor incidence in animals fed with the orange peel extract containing the 14 methoxyflavones, as opposed to 100% tumor incidence in control animals. See also the specification, for example, at page 5 line 7 through page 9, line 13, wherein further working examples employing the claimed extract in the treatment or prevention of cancer are provided. The *in vivo* and *in vitro* tumor models used in the present invention are art recognized animal cancer models for demonstrating the prevention and treatment of cancer.

Notwithstanding, without conceding the validity of the rejection, and solely to expedite the prosecution of this application, Applicant has amended pertinent claims to recite “treatment” or “reducing the incidence” of cancer. Accordingly, Applicant respectfully requests reconsideration and removal of this rejection, as the claims conform with the requirements of 35 U.S.C. § 112, ¶ 1.

IV. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 2-11 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner avers that “[c]laims 2, 4 and 6-11 are rendered vague and indefinite by the term ‘extract’ because this term, in and of itself, does not adequately delineate its metes and bounds.” Applicant respectfully traverses the rejection for at least the following reasons:

The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification. *Orthokinetics, Inc., v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q. 2d 1081 (Fed. Cir. 1986). Applicant respectfully submits that one skilled in the art would understand the metes and bounds of claims 2, 4 and 6-11, when read in light of the specification and the teachings of the prior art available to the skilled artisan.

The specification, for example, at page 11, line 9 through page 14, line 10 provides description about compositions containing at least one of rosemary extract, a Mexican Bamboo extract, a Huzhang extract, and a black tea extract recited in claims 2 and 6 for inhibiting tumor cell growth or prevention of cancer. The term “extract” is a commonly understood term and is used in the prior art. For example, the prior art references cited by the Examiner in the Office Action and those referred to in the specification use the term extract and teach that the extracts can be used for inhibiting tumor cell growth or prevention of cancer. Specifically, for example, Pierce teaches rosemary extract, Madis Botanicals teaches a Huzhang extract and a Mexican Bamboo extract, Castelman teaches black tea extract. Thus, Applicant respectfully submits that the metes and bounds or the meaning of the term “extract” in the context of the present invention is reasonably discernible from the teachings in the specification and the prior art available to the persons of skill in the pertinent field.

Applicant notes the Examiner’s statement, on page 4 of the Office Action, that “[t]his term is best defined as a product-by-process,” Applicant also notes the case (*In re van Geuns*, 988 F.2d 1181 (Fed. Cir. 1993) cited by the Examiner on page 5 of the Office Action in support of the rejection. The *Geuns* case is not about indefiniteness of a claim term. It is about obviousness issue, where the patentee sought to have the phrase “uniform magnetic field” construed narrowly so that it is limited to NMR (nuclear magnetic resonance) imaging. It is in this context, the court stated that “limitations are not to be read into the claims from the specification.” This case does not stand for a proposition that the term “extract” in a composition claim is indefinite.

Applicant respectfully submits that the term “extract” is a definite term even when used in composition claims in view of the prior art and the status of the art. Indeed, a number of patents have been issued to date with composition claims reciting the term “extract.” See, for example, U.S. Patents 6,197,309 (claiming a composition comprising Pygeum extract for prevention or improvement of prostrate disorders), 6,706,256 (claiming a composition comprising an extract of Citrus and Vitis plants for use as an antibacterial) and 6,719,966 (claiming a composition comprising a botanical extract for use as an antiperspirant/deodorant).

Copies of these three U.S. Patents are attached herewith as Exhibit 1. Further, for purposes of completeness only, Applicant notes breadth of a claim is not to be construed as indefiniteness.

Accordingly, Applicant respectfully requests reconsideration and removal of the rejection as claims 2-11 conform with the requirements of 35 U.S.C. § 112, ¶ 2.

V. Rejection Under 35 U.S.C. §102

Claim 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by Nagy et al. (Citrus Science and Technology, 1997, AVI, Westport, Volume 1, pages 416-417). Claims 1, 3, 5, 7-8 and 10-11 stand rejected under 35 U.S.C. §102(b) as being anticipated by Attaway (1994, Citrus Science and Properties, Food Phytochemicals for Cancer Prevention, ACS Symposia Series, section 546, pages 240 –248). These rejections are respectfully traversed and believed overcome in view of the following discussion:

A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim. *Bristol-Myers Squibb v. Ben Venue*, 246 F.3d 1368 (Fed. Cir. 2001); *Schering Corporatin v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003). Identity of invention requires that a prior reference disclose to one of ordinary skill in the art all elements and limitations of the patent claim. *Scripps Clinic v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81 (Fed. Cir. 1986). Inherent anticipation requires that the missing descriptive material is “necessarily present,” not merely, probably or possibly present in the prior art reference. *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999). Even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling. *Elan Pharmaceuticals v. Athena Neurosciences* 346 F.3d 1051 (Fed. Cir. 2003).

Nagy

Nagy provides a description of the flavonoids that occur in citrus fruits and leaves, and lists a number methoxylated flavones. It lists each compound by the common name and well as by its systematic name.

Claim 1 requires “. . . an extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of 4', 5, 6, 7, 8-pentamethoxyflavone [and 13 other specific] . . . methoxyflavone[s], and a physiologically acceptable carrier or excipient.”

The Examiner asserts that “Nagy et al. inherently teach a composition comprising at least three polymethoxylated flavones in a physiologically acceptable carrier or excipient (i.e., citrus juice or water).”

The Examiner appears to be arguing that the claim reciting the three or more naturally occurring chemical compounds (i.e., the methoxyflavones) is unpatentable over a naturally occurring composition [i.e., citrus fruit or different *Citrus* varieties] containing those compounds.

Applicant respectfully submits that it does not claim a methoxyflavone *per se* nor a composition encompassing citrus fruit or a *Citrus* variety in its natural state but instead seeks “. . . an extract of orange² peel containing three or more polymethoxylated flavones . . . selected from the group consisting of . . . methoxyflavone[s], and a physiologically acceptable carrier or excipient.” Inherent anticipation requires that this missing descriptive material is “necessarily present,” not merely, probably or possibly present in the Nagy reference. Since the claim 1 does not encompass natural compositions, in that “an extract of orange peel” does not necessarily occur in nature, and Nagy does not teach the extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of . . . methoxyflavone[s], the inherency test is not met.

Further, the Examiner has not established that Nagy is an enabling prior art reference. As such, the Examiner has not established a *prima facie* case of anticipation in support of the

² *Citrus sinensis*

rejection of claims 1 based on Nagy. Therefore, in contrary to the Examiner's assertion, Nagy does not anticipate claim 1 as it does not teach or disclose each and every limitation of this claim.

Attaway

Attaway discloses biological activities, anticarcinogenic and antitumor activities, of citrus flavonoids. This reference teaches that polymethoxylated flavonoids, nobiletin and tangeritin, markedly inhibited cell growth (see, Attaway, at page 245, lines 1-2) and tangeretin was the most potent of all citrus flavonoids tested for ability to the invasion of malignant mouse tumor cells. See, Attaway, at page 246, second full paragraph. See also, text at page 246 last paragraph discussing the effectiveness of tangeritin.

The rejection based on Attaway also depends on inherent anticipation. Specifically, the Examiner asserts on page 5 of the Office Action that “[s]ince citrus juice are taught to have these flavonoids possessing said activity, inherently, Attaway teaches a composition comprising polymethoxyflavonoids in a physiologically acceptable carrier or excipient.”

Applicant respectfully submits that it does not claim a methoxyflavone *per se* nor citrus juice, nor even a composition encompassing citrus fruit or a *Citrus* variety in its natural state but instead seeks, in claim 1, “. . . an extract of orange³ peel containing three or more polymethoxylated flavones . . . selected from the group consisting of [14 specific] . . . methoxyflavone[s], and a physiologically acceptable carrier or excipient.” Inherent anticipation requires that this missing descriptive material is “necessarily present,” not merely, probably or possibly present in the Attaway reference. Since the claims do not encompass natural compositions, in that “an extract of orange peel” does not necessarily occur in nature and Attaway does not teach the extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of [the 14 specific] . . . methoxyflavone[s], the inherency test is not met.

Further, the Examiner has not established that Attaway is an enabling prior art reference.

³ *Citrus sinensis*

In support of the rejection based on Attaway, the Examiner also cites Malterud et al., J. Agric. Food Chem., 2000, 48:5576-5580. The Malterud reference, which is not available as prior art, teaches the isolation and use of the individual polymethoxylated flavones such as sinensetin, nobiletin, tangeretin as inhibitors of 15-lipoxygenase, an enzyme implicated in the development of atherosclerosis. Malterud provides no evidence that Attaway inherently teaches an extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of [the 14 specific] . . . methoxyflavone[s].

As such, the Examiner has not established a *prima facie* case of anticipation in support of the rejection of claim 1 and 8 based on Attaway with or without evidence from Malterud. Therefore, in contrary to the Examiner's assertion, Attaway does not anticipate claim 1 as it does not teach or disclose each and every limitation in claim 1. Claims 3, 5, 7-8 and 10-11 by virtue of their dependency from claim 1, are similarly considered by Applicant to patentably define themselves and are novel over Attaway.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102 (b) are respectfully requested.

VI. Rejection Under 35 U.S.C. §103

Claims 1-11 stand rejected as allegedly being obvious over Nagy et al., (1997, Citrus Science and Technology, AVI, Westport, Volume 1, pages 416-417) and Attaway (1994, Citrus Science and Properties, Food Phytochemicals for Cancer Prevention, ACS Symposia Series 546, pages 240 –248) with evidence from Malterud et al. (2000, J. Agric. Food Chem., 48:5576-5580) in view of Pierce (The American Pharmaceutical Association Practical Guide to Natural Medicines, 1999, Stonesong Press, Inc., pages 563-566) Madis Botanicals (1997, Madis Botanicals, Inc., Resverapure[®] Resveratrol PE 8%, Product Code 04544, page 2, lines 6-7 and 15-31), Castleman (1991, The Healing Herbs, The Ultimate Guide to the Curative Power of Nature's Medicines, Rodal Press, Emmaus, PA, page 349, Column 2, lines 3-10), Thomas (U.S. Patent 5,830,738) and Bailey (U.S. Patent 5,859,293). These rejections are respectfully traversed and believed overcome in view of the following discussion:

The Examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of going forward with evidence or argument shift to the Applicant. *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). The test of obviousness is “whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention.” *In re Gorman*, 933 F.2d 982 (Fed. Cir. 1991). Furthermore, to establish *prima facie* case of obviousness under § 103, the Federal Circuit requires, *inter alia*, satisfaction of two factors: (1) whether the cited combination of references would have suggested to those of ordinary skill in the art that they should make the claimed composition or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. *Id*; *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998).

Nagy, Attaway and Malterud references are discussed above.

Thomas is cited for teaching carotenoid pigments obtained from orange peels and their use in preventing cancer. Pierce is cited for teaching rosemary extract and its use in fighting cancer. Madis Botanicals is cited for teaching resveratrol from Huzhang. Madis Botanicals is also cited for teaching Mexican bamboo as *Polygonum cuspidatum*. Castleman is cited for teaching black tea extract and its use in cancer prevention.

From these references, the Examiner concludes that a person of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings from the cited prior art references to obtain a composition comprising extract from orange peel containing at least three flavones and to administer the composition to an individual to treat cancer or inhibit tumor growth.

Claim 1 is a composition and requires “. . . an extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of 4', 5, 6, 7, 8 - pentamethoxyflavone, [and 13 other specific] . . . methoxyflavone[s], and a physiologically acceptable carrier or excipient.”

Claim 2 is also directed to a composition and it requires “the extract of claim 1 and at least one other compound selected from the group consisting of rosemary extract, a Mexican Bamboo extract, a Huzhang extract, resveratrol, a black tea extract, and a hydroxylated or methoxylated resveratrol analog.”

Claim 3, which is directed to a method for inhibiting tumor cell growth in an animal, requires “administering to an animal the extract of claim 1.”

The remaining claims, which are dependent claims, require the composition of claim 1 or the composition of claim 1 and at least one additional compound as set forth in claim 2.

Applicant respectfully disagrees with the Examiner’s superficial and self serving conclusion to the extent Examiner wishes to assert obviousness of the specific composition claims or methods using the claimed compositions because the Examiner has not established that the requirements of obviousness under § 103 have been met. As such, the Examiner has not established a *prima facie* case of obviousness in support of his rejection of the independent claim 1 and, therefore, the rejection should be withdrawn.

Specifically, one of ordinary skill in the art would find neither a suggestion nor motivation to obtain the claimed compositions and to administer the claimed composition to an individual to treat cancer or inhibit tumor growth because the cited references when taken alone or in combination do not teach or suggest the claimed compositions and their use in preventing, treating or inhibiting cancer.

Of the cited references, the Nagy and Attaway (with evidence from Malterud) references provide a review of the various methoxyflavones found in *Citrus* species and various uses thereof including cancer treatment (Attaway) or atherosclerosis (with evidence from Malterud). These references teach or suggest the use of the individual methoxyflavones found in *Citrus*. Applicant respectfully submits that its claims are not directed to a methoxyflavone *per se* nor a composition encompassing any orange peel extract, the orange peel, citrus fruit or a *Citrus* variety in its natural state. The Nagy and Attaway references do not teach or suggest compositions with “an extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of 4', 5, 6, 7, 8 - pentamethoxyflavone, [and 13 other specific] . . .

methoxyflavone[s]. The inherency test is not met (as discussed under subsection V above) and the Examiner provided no basis, found in that prior art, for selecting the specific orange peel extract and using it in compositions such as those claimed by the Applicant.

Contrary to the Examiner's assertions, the Attaway (with evidence from Malterud), Thomas, Pierce, Madis Botanicals and/or Castleman references fail to make up for the deficiency in the Nagy in arriving at the claimed compositions or methods. These references do not teach or suggest, either alone or in combination, methods of treating cancer using "an extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of 4', 5, 6, 7, 8 - pentamethoxyflavone, [and 13 other specific] . . . methoxyflavone[s] . . ." If anything, upon consulting the Attaway reference, one skilled in the art would be led in a direction different from that taken by the Applicant. Specifically, Attaway, at page 246, paragraph 2, states that "[t]angeretin was the most potent of all citrus flavonoids [including hesperidin, naringin, nobiletin] tested [in isolation] for ability to inhibit the invasion of malignant mouse tumor cells (MO₄) into normal tissue . . ." Thus, Attaway suggests that further experimentation to treat cancer should be carried out using tangeretin, not the compositions claimed by the Applicant. See also, the last sentence on page 246 of Attaway. The Thomas references focuses on the extraction of carotenoid pigments, not on the extraction of methoxyflavones, from orange peels and contemplates their use in preventing some forms of cancer.

Thus, contrary to the Examiner's assertion, the secondary references do not make up the deficiency in the Nagy reference, and cited combination of references would not have suggested to those of ordinary skill in the art that they should make the claimed composition or carry out the claimed process.

There must also be a reasonable expectation that the proposed modification or combination will be successful. There is no reasonable expectation that one skilled in the art, by combining the teachings from the cited prior art references, would be able to obtain, for example, the "extract of orange peel containing three or more polymethoxylated flavones . . . selected from the group consisting of 4', 5, 6, 7, 8 - pentamethoxyflavone, [and 13 other specific] . . .

methoxyflavone[s] . . .” Even if all of the methoxyflavones found in *Citrus* were in the prior art, those methoxyflavones are quite mute in directing one having ordinary skill in the art to the claimed extract for any purpose. Applicant recognizes that obviousness does not require complete predictability, but it is necessary, even once the methoxyflavones are known, that the cited references or other prior art themselves further provide some predictability in selecting the specific orange peel extract, and that the extract is a significant orange peel extract. In fact, the expectation would most likely be that the combination or modification would completely fail because the cited references do not provide an enabling description of the specific extract set forth in claim 1 or its use. Thus, the reasonable expectation of success requirement can not be satisfied as well.

The teaching or suggestion to make the claimed composition or carry out the claimed process and the reasonable expectation of success must both be found in the cited art, and not be based on Applicant’s disclosure. As discussed above, the Examiner has not shown that the cited art provides suggestion or motivation to one of ordinary skill in the art to make the claimed composition or carry out the claimed process and in so making or carrying out one would have the reasonable expectation of success. Stated otherwise, lacking a suggestion or motivation and reasonable expectation of success, Applicant believes that the Examiner selected these references with the help of hindsight⁴.

In view of the foregoing, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of the independent claim 1, based on the combination of the cited references, under 35 U.S.C. § 103(a). Even if *prima facie* obviousness has been established, which it has not, it is urged that the cited art nonetheless fails to render the present invention obvious under a proper § 103 analysis, as the proper suggestions and motivations to combine the cited references are lacking.

Applicant also submits that the Examiner has not established a *prima facie* case of obviousness of dependent claims 2-11 under 35 U.S.C. § 103(a). In particular, rejected

⁴ Use of hindsight in the selection of references to establish a case of obviousness is improper. *In re Gorman*, 18 USPQ2d 1885 (Fed. Cir. 1991).

dependent claims 2-11, by virtue of their dependency from the corresponding independent claim 1, are similarly considered by Applicant to patentably define themselves over the cited references. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

VII. New Presented Claims 12-21

Claims 12-21 have been added to the application to recite novel features disclosed in the specification. Both Nagy and Attaway (with evidence from Malterud) do not disclose the compositions and methods defined in new claims 12-21. For example, both Nagy and Attaway do not disclose the specific orange peel extract with 14 specific methoxyflavones or a mixture of isolated 5,6,7,8,3',4'-hexamethoxyflavone and 5,6,7,8,4'-pentamethoxyflavone.

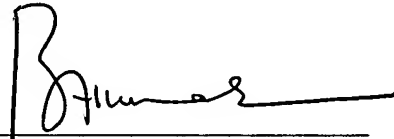
Further, Nagy, Attaway (with evidence from Malterud) Pierce, Madis Botanicals, Castleman, Thomas and Bailey do not, either singly or in combination, teach or suggest the compositions or methods defined in new claims 12-21. Therefore, the invention defined in these new claims is not obvious from the cited prior art.

VIII. Conclusion

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of all of the pending claims are earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the present application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'W. McNichol, Jr.', written over a horizontal line.

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